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(54) Title: SULFONAMIDES

(57) Abstract: The present invention relates to sulfonamides, pharmaceutical compositions containing them, and their use as antagonists of urotensin II.

SULFONAMIDES

FIELD OF THE INVENTION

The present invention relates to sulfonamides, pharmaceutical compositions containing them and their use as urotensin II antagonists

BACKGROUND OF THE INVENTION

The integrated control of cardiovascular homeostasis is achieved through a combination of both direct neuronal control and systemic neurohormonal activation. Although the resultant release of both contractile and relaxant factors is normally under stringent regulation, an aberration in this *status quo* can result in cardiohemodynamic dysfunction with pathological consequences.

The principal mammalian vasoactive factors that comprise this neurohumoral axis, namely angiotensin-II, endothelin-1, norepinephrine, all function via an interaction with specific G-protein coupled receptors (GPCR). Urotensin-II, represents a novel member of this neurohumoral axis.

In the fish, this peptide has significant hemodynamic and endocrine actions in diverse end-organ systems and tissues:

- smooth muscle contraction

  both vascular and non-vascular in origin including smooth muscle preparations from the gastrointestinal tract and genitourinary tract. Both pressor and depressor activity has been described upon systemic administration of exogenous peptide

- osmoregulation:

  effects which include the modulation of transepithelial ion (Na^+, Cl^-) transport. Although a diuretic effect has been described, such an effect is postulated to be secondary to direct renovascular effects (elevated GFR)

- metabolism:

  urotensin-II influences prolactin secretion and exhibits a lipolytic effect in fish (activating triacylglycerol lipase resulting in the mobilization of non-esterified free fatty acids)

  (Pearson, *et. al. Proc. Natl. Acad. Sci. (U.S.A.)* **1980**, *77*, 5021; Conlon, *et. al. J. Exp. Zool.* **1996**, *275*, 226.)

In studies with human Urotensin-II it was found that it:

- was an extremely potent and efficacious vasoconstrictor
- exhibited sustained contractile activity that was extremely resistant to wash out
- had detrimental effects on cardiac performance (myocardial contractility)

Human Urotensin-II was assessed for contractile activity in the rat-isolated aorta and was shown to be the most potent contractile agonist identified to date. Based on the *in vitro* pharmacology and *in vivo* hemodynamic profile of human Urotensin-II it plays a pathological role in cardiovascular diseases characterized by excessive or abnormal vasoconstriction and myocardial dysfunction. (Ames *et. al. Nature* **1999**, *401*, 282; Douglas & Ohlstein (2001). Trends Cardiovasc. Med., 10: in press).

Compounds that antagonize the Urotensin-II receptor may be useful in the treatment of congestive heart failure, stroke, ischemic heart disease (angina, myocardial ischemia), cardiac arrhythmia, hypertension (essential and pulmonary), COPD, fibrosis (e.g. pulmonary fibrosis), restenosis, atherosclerosis, dyslipidemia, asthma, (Hay DWP, Luttmann MA, Douglas SA: 2000, Br J Pharmacol: **131; 10-12**) neurogenic inflammation and metabolic vasculopathies all of which are characterized by abnormal vasoconstriction and/or myocardial dysfunction. Urotensin antagonists may provide end organ protection in hypersensitive cohorts in addition to lowering blood pressure.

Since U-II and GPR14 are both expressed within the mammalian CNS (Ames *et. al. Nature* **1999**, *401*, 282), they also may be useful in the treatment of addiction, schizophrenia, cognitive disorders/Alzheimers disease, (Gartlon J. Psychopharmacology (Berl) 2001 June; 155(4):426-33), impulsivity, anxiety, stress, depression, pain, migraine, neuromuscular function, parkinsons, movement disorders, sleep-wake cycle, and incentive motivation (Clark *et al.Brain Research* 923 (2001) 120-127.

Functional U-II receptors are expressed in rhabdomyosarcomas cell lines and therefore may have oncological indications. Urotensin may also be implicated in various metabolic diseases such as diabetes (Ames *et. al. Nature* **1999**, *401*, 282, Nothacker et al., *Nature Cell Biology* 1: 383-385, 1999) and in various gastrointestinal disorders, bone, cartilage, and joint disorders (e.g. arthritis and osteoporosis); and genito-urinary disorders. Therefore, these compounds may be useful for the prevention (treatment) of gastric reflux, gastric motility and ulcers, arthritis, osteoporosis and urinary incontinence.

SUMMARY OF THE INVENTION

In one aspect this invention provides for sulfonamides and pharmaceutical compositions containing them.

In a second aspect, this invention provides for the use of sulfonamides as antagonists of urotensin II, and as inhibitors of urotensin II.

In another aspect, this invention provides for the use of sulfonamides for treating conditions associated with urotensin II imbalance.

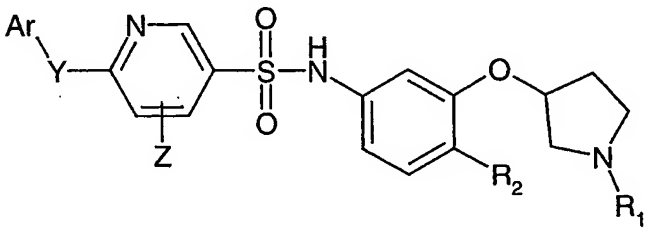
In yet another aspect, this invention provides for the use of sulfonamides for the treatment of congestive heart failure, stroke, ischemic heart disease (angina, myocardial ischemia), cardiac arrhythmia, hypertension (essential and pulmonary), renal disease (acute and chronic renal failure/end stage renal disease) along with peripheral vascular disease (male erectile dysfunction, diabetic retinopathy, intermittent claudication/ischemic limb disease) and ischemic/hemorrhagic stroke, COPD, restenosis, asthma, neurogenic inflammation, migraine, metabolic vasculopathies, bone/cartilage/joint diseases, arthritis and other inflammatory diseases, fibrosis (e.g. pulmonary fibrosis), sepsis, atherosclerosis, dyslipidemia, addiction, schizophrenia, cognitive disorders/Alzheimers disease, impulsivity, anxiety, stress, depression, parkinsons, movement disorders, sleep-wake cycle, incentive motivation, pain, neuromuscular function, diabetes, gastric reflux, gastric motility disorders, ulcers and genitourinary diseases.

The urotensin antagonist may be administered alone or in conjunction with one or more other therapeutic agents, said agents being selected from the group consisting of endothelin receptor antagonists, angiotensin converting enzyme (ACE) inhibitors, A-II receptor antagonists, vasopeptidase inhibitors, diuretics, digoxin, and dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonists.

Other aspects and advantages of the present invention are described further in the following detailed description of the preferred embodiments thereof.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides for compounds of Formula (I):



Formula (I)

wherein:

Ar is phenyl substituted or unsubstituted by one or two of the following: halogen, CN, $S(C_{1-6}$ alkyl), CF_3, OCF_3, SCF_3, C_{1-6} alkyl, C_{1-6} alkoxy, $CO_2(C_{1-6}$ alkyl), or NO_2;

Y is O or S;

Z is hydrogen, halogen, or C_{1-6} alkyl;

R_2 is hydrogen, halogen, CN, or C_{1-4} alkyl;

R_1 is hydrogen or C_{1-6} alkyl;

or a pharmaceutically acceptable salt thereof.

When used herein, the term "alkyl" includes all straight chain and branched isomers. Representative examples thereof include methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *t*-butyl, *n*-pentyl and *n*-hexyl.

When used herein, the terms 'halogen' and 'halo' include fluorine, chlorine, bromine and iodine, and fluoro, chloro, bromo, and iodo, respectively.

Preferred substituents for Ar are halogen or C_{1-6} alkoxy.

Z is preferably halogen or hydrogen.

R_2 is preferably halogen or hydrogen.

R_1 is preferably C_{1-3} alkyl.

Especially preferred compounds are :

5-bromo-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-6-[(2,3-dichlorophenyl)thio]-3-pyridinesulfonamide;

5-bromo-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-6-[(3,5-dichlorophenyl)thio]-3-pyridinesulfonamide;

6-{[3,4-bis(methyloxy)phenyl]thio}-5-bromo-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-3-pyridinesulfonamide;

5-bromo-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-6-[(3,5-dichlorophenyl)oxy]-3-pyridinesulfonamide;

5-bromo-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-6-[(3,5-difluorophenyl)oxy]-3-pyridinesulfonamide;

6-{[3,4-bis(methyloxy)phenyl]oxy}-5-bromo-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-3-pyridinesulfonamide;

5-bromo-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-6-{[3-(methyloxy)phenyl]oxy}-3-pyridinesulfonamide;

5-bromo-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-6-{[4-(methyloxy)phenyl]oxy}-3-pyridinesulfonamide;

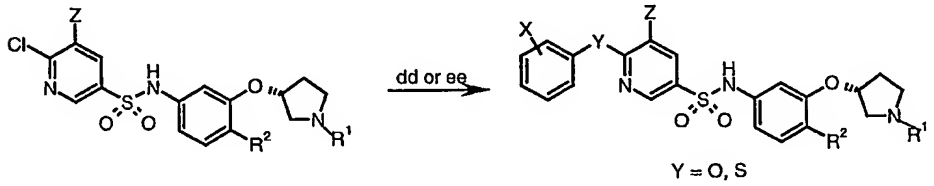
5-bromo-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-6-[(3,4-dichlorophenyl)oxy]-3-pyridinesulfonamide; and

5-bromo-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-6-[(2,3-dichlorophenyl)oxy]-3-pyridinesulfonamide.

The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active form. All of these compounds and their diastereoisomers are contemplated to be within the scope of the present invention.

Compounds of Formula (I) may be prepared as outlined in Scheme 1. Starting compounds 1 may be prepared as outlined in WO 289793, incorporated by reference herein.

Scheme 1

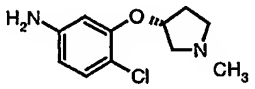


1 2

dd) phenol or thiophenol, NaH, DMF, heat; ee) phenol or thiophenol, NaH, Cs_2CO_3, DMF, heat.

Y, Z, R^1 and R^2 are as described in Formula I X are the substiuents listed for Ar.

Aniline B has been previously described in published application WO 2002089792 A1 incorporated by reference herein.



Anline **B**

Sulfonyl chlorides, when not commercially available, can prepared by methods known in the art: Shahripour, A.B. et al. *Bioorg. Med. Chem.* **2002**, *10*, 31; Cross, P.E. et al. *J. Med. Chem.* **1978**, *21*, 845; Huntress et al *J. Amer. Chem. Soc.* **1941**, *63*, 3446; Hashimoto, H. et al *J. Med. Chem.* **2002**, *45*, 1511; O'Brien, P. M. et al. *J.Med.Chem.* **2000**, *43*, 156; Brundish, D. *J.Med.Chem.* **1999**, *22*, 4584.

Substituted benzenesulfonyl chlorides used in the synthesis of the title compounds which were not available commercially were prepared by methods known to those practiced in the art.

With appropriate manipulation, including the use of alternative nitrogen protecting group(s), the synthesis of the remaining compounds of Formula (I) was accomplished by methods analogous to those above and to those described in the Experimental section.

In order to use a compound of the Formula (I) or a pharmaceutically acceptable salt thereof for the treatment of humans and other mammals it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Compounds of Formula (I) and their pharmaceutically acceptable salts may be administered in a standard manner for the treatment of the indicated diseases, for example orally, parenterally, sub-lingually, transdermally, rectally, via inhalation or via buccal administration.

Compounds of Formula (I) and their pharmaceutically acceptable salts which are active when given orally can be formulated as syrups, tablets, capsules and lozenges. A syrup formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, peanut oil, olive oil, glycerine or water with a flavoring or coloring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used. Examples of such carriers include magnesium stearate, terra alba, talc, gelatin, agar, pectin, acacia, stearic acid, starch, lactose and sucrose. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates or oils and are incorporated in a soft gelatin capsule shell.

Typical parenteral compositions consist of a solution or suspension of the compound or salt in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil, for example polyethylene glycol, polyvinylpyrrolidone, lecithin, arachis oil, or sesame oil.

Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be administered as a dry powder or in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane or trichlorofluoromethane.

A typical suppository formulation comprises a compound of Formula (1) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent, for example polymeric glycols, gelatins, cocoa-butter or other low melting vegetable waxes or fats or their synthetic analogues.

Typical transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer to themselves a single dose.

Each dosage unit for oral administration contains suitably from 0.1 mg to 500 mg/Kg, and preferably from 1 mg to 100 mg/Kg, and each dosage unit for parenteral administration contains suitably from 0.1 mg to 100 mg, of a compound of Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free acid. Each dosage unit for intranasal administration contains suitably 1-400 mg and preferably 10 to 200 mg per person. A topical formulation contains suitably 0.01 to 1.0% of a compound of Formula (I).

The daily dosage regimen for oral administration is suitably about 0.01 mg/Kg to 40 mg/Kg, of a compound of Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free acid. The daily dosage regimen for parenteral administration is suitably about 0.001 mg/Kg to 40 mg/Kg, of a compound of the Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free acid. The daily dosage regimen for intranasal administration and oral inhalation is suitably about 10 to about 500 mg/person. The active ingredient may be administered from 1 to 6 times a day, sufficient to exhibit the desired activity.

These sulphonamide analogs may be used for the treatment of congestive heart failure, stroke, ischemic heart disease (angina, myocardial ischemia), cardiac arrhythmia, hypertension (essential and pulmonary), renal disease (acute and chronic renal failure/end stage renal disease) along with peripheral vascular disease (male erectile dysfunction, diabetic retinopathy, intermittent claudication/ischemic limb disease) and ischemic/hemorrhagic stroke, COPD, restenosis, asthma, neurogenic inflammation, migraine, metabolic vasculopathies, bone/cartilage/joint diseases, arthritis and other inflammatory diseases, fibrosis (e.g. pulmonary fibrosis), sepsis, atherosclerosis, dyslipidemia, addiction, schizophrenia, cognitive disorders/Alzheimers disease, impulsivity, anxiety, stress, depression, pain, neuromuscular function, diabetes, gastric reflux, gastric motility disorders, ulcers and genitourinary diseases.

The urotensin antagonist may be administered alone or in conjunction with one or more other therapeutic agents, said agents being selected from the group consisting of endothelin receptor antagonists, angiotensin converting enzyme (ACE) inhibitors, A-II receptor antagonists, vasopeptidase inhibitors, diuretics, digoxin, and dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonists.

No unacceptable toxicological effects are expected when compounds of the invention are administered in accordance with the present invention.

The biological activity of the compounds of Formula (I) are demonstrated by the following tests:

Radioligand binding:

HEK-293 cell membranes containing stable cloned human and rat GPR-14 (20 ug/assay) were incubated with 200 pM [125I] h-U-II (200 Ci/mmol^{-1} in the presence of increasing concentrations of test compounds in DMSO (0.1 nM to 10 uM), in a final incubation volume of 200 ul (20 mM Tris-HCl, 5 mM MgCl2). Incubation was done for 30 minutes at room temperature followed by filtration GF/B filters with Brandel cell harvester. ^{125}I labeled U-II binding was quantitated by gamma counting. Nonspecific binding was defined by ^{125}I U-II binding in the presence of 100 nM of unlabeled human U-II. Analysis of the data was performed by nonlinear least square fitting.

Ca^{2+}-mobilization:

A microtitre plate based Ca^{2+}-mobilization FLIPR assay (Molecular Devices, Sunnyvale, CA) was used for the functional identification of the ligand activating HEK-293 cells expressing (stable) recombinant GPR-14. The day following transfection, cells were plated in a poly-D-lysine coated 96 well black/clear plates. After 18-24 hours the media was aspirated and Fluo 3AM-loaded cells were exposed to various concentrations (10 nM to 30 uM) of test compounds followed by h-U-II. After initiation of the assay, fluorescence was read every second for one minute and then every 3 seconds for the following one minute. The inhibitory concentration at 50% (IC50)was calculated for various test compounds.

Inositol phosphates assays:

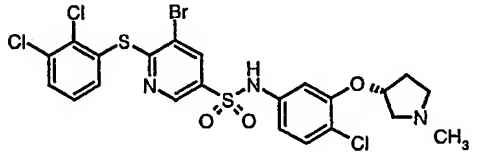
HEK-293-GPR14 cells in T150 flask were prelabeled overnight with 1 uCi myo-[^{3}H] inositol per ml of inositol free Dulbecco's modified Eagel's medium. After labeling, the cells were washed twice with Dulbecco's phosphate-buffered saline (DPBS) and then incubated in DPBS containing 10 mM LiCl for 10 min at 37°C. The experiment was initiated by the addition of increasing concentrations of h-U-II (1 pM to 1μM) in the absence and presence of three different concentrations (0.3, 1 and 10 uM) of test compounds and the incubation continued for an additional 5 min at 37°C after which the reaction was terminated by the addition of 10% (final concentration) trichloroacetic acid and centrifugation. The supernatants were neutralized with 100ul of 1M Trizma base and the inositol phosphates were separated on AG 1-X8 columns (0.8 ml packed, 100-200 mesh) in formate phase. Inositol monophosphate was eluted with 8 ml of 200 mM ammonium formate. Combined inositol di and tris phosphate was eluted with 4ml of 1M ammonium formate/ 0.1 M formic acid. Eluted fractions were counted in beta scintillation counter. Based on shift from the control curve K_B was calculated.

Activity for the compounds of this invention range from (radioligand binding assay): Ki = 1 nM – 1000 nM.

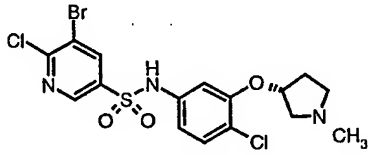
The following Examples are illustrative but not limiting embodiments of the present invention.

Example 1

5-bromo-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-6-[(2,3-dichlorophenyl)thio]-3-pyridinesulfonamide



1a) 5-bromo-6-chloro-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl] oxy}phenyl)-3-pyridinesulfonamide



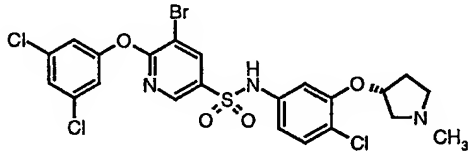
Aniline **B** (1.2 g, 5.29 mmol) was dissolved in 11 mL of methylene chloride, 30 mL of carbon tetrachloride, and pyridine (0.428 mL, 5.29 mmol) and treated with a solution of 5-bromo-6-chloro-3-pyridinesulfonyl chloride (1.54 g, 5.29 mmol) dissolved in 4 mL of methylene chloride and 5 mL of carbon tetrachloride with vigorous stirring at room temperature. The reaction mixture was maintained for 18 hours, and then the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (35 g Redisep column, silica, 40 um, 60 Å, 35 mL/min, A: MeOH, B: CH_2Cl_2, A: 0% for 20 min, 0% to 10% over 10 min, 10% for 20 min, 10% to 30% over 20 min, 30% for 15 min, 30% to 50% over 2 min, 50% for 10 min; detection at 214 nm) to give 1.14 g (45%) of the title compound as an orange solid. MS (ES) m/e 480 $[M+H]^+$

1b) 5-bromo-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-6-[(2,3-dichlorophenyl)thio]-3-pyridinesulfonamide

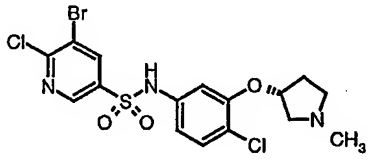
2,3-dichlorobenzenethiol (41.0 mg, 0.229 mmol) was dissolved in 1 mL of anhydrous 1-methyl-2-pyrrolidinone and treated with NaH (60 % dispersion in mineral oil, 10.0 mg, 0.250 mmol). After all bubbling had stopped, the reaction was stirred for an additional 30 minutes and treated with a solution of 5-bromo-6-chloro-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-3-pyridinesulfonamide (100.0 mg, 0.208 mmol) in 1.0 mL of anhydrous 1-methyl-2-pyrrolidinone. The reaction was heated at 125 °C for eighteen hours, cooled to room temperature, filtered through a 0.2 micron Acrodisk, and purified by preparative HPLC (YMC CombiPrep ODS-A, 50 x 20 mm, 20 mL/min, A: acetonitrile B: water, A: 5% to 95% during 15 min, UV detection at 214 nm) to give 92.5 mg (71 %) of the title compound as a brown solid. MS (ES) m/e 624 $[M+H]^+$

Example 2

5-bromo-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-6-[(3,5-dichlorophenyl)oxy]-3-pyridinesulfonamide



2a) 5-bromo-6-chloro-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl] oxy}phenyl)-3-pyridinesulfonamide



Aniline B (1.2 g, 5.29 mmol) was dissolved in 11 mL of methylene chloride, 30 mL of carbon tetrachloride, and pyridine (0.428 mL, 5.29 mmol) and treated with a solution of 5-bromo-6-chloro-3-pyridinesulfonyl chloride (1.54 g, 5.29 mmol) dissolved in 4 mL of methylene chloride and 5 mL of carbon tetrachloride with vigorous stirring at room temperature. The reaction mixture was maintained for 18 hours, and then the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (35 g Redisep column, silica, 40 um, 60 Å, 35 mL/min, A: MeOH, B: CH_2Cl_2, A: 0% for 20 min, 0% to 10% over 10 min, 10% for 20 min, 10% to 30% over 20 min, 30% for 15 min, 30% to 50% over 2 min, 50% for

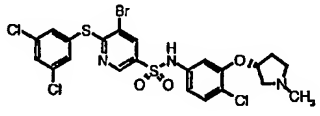
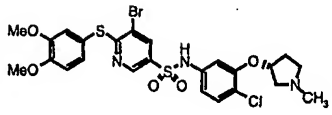
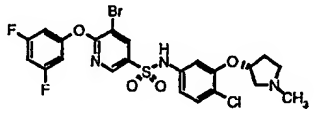
10 min; detection at 214 nm) to give 1.14 g (45%) of the title compound as an orange solid. MS (ES) m/e 480 $[M+H]^+$

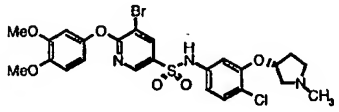
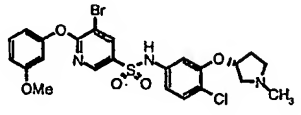
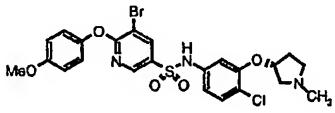
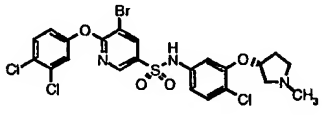
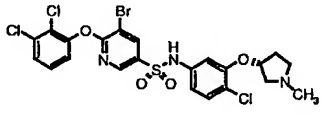
2b) 5-bromo-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-6-[(3,5-dichlorophenyl)oxy]-3-pyridinesulfonamide

3,5-dichlorophenol (136.0 mg, 0.832 mmol) was dissolved in 1 mL of anhydrous 1-methyl-2-pyrrolidinone and treated with NaH (60 % dispersion in mineral oil, 35.0 mg, 0.874 mmol). After all bubbling had stopped, the reaction was stirred for an additional 30 minutes and treated with a solution of 5-bromo-6-chloro-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-3-pyridinesulfonamide (100.0 mg, 0.208 mmol) in 1.0 mL of anhydrous 1-methyl-2-pyrrolidinone. The reaction was heated at 125 °C for eighteen hours, cooled to room temperature, filtered through a 0.2 micron Acrodisk, and purified by preparative HPLC (YMC CombiPrep ODS-A, 50 × 20 mm, 20 mL/min, A: acetonitrile B: water, A: 5% to 95% during 15 min, UV detection at 214 nm) to give 19.4 mg (15 %) of the title compound as a brown solid. MS (ES) m/e 606 $[M+H]^+$

Example 3- 10

The following compounds were prepared by a method similar to the one described in Examples 1 and 2 using the appropriate phenols or benzenethiols:

#	structure	name	m/z
3		5-bromo-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-6-[(3,5-dichlorophenyl)thio]-3-pyridinesulfonamide	624
4		6-{[3,4-bis(methyloxy)phenyl]thio}-5-bromo-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-3-pyridinesulfonamide	614
5		5-bromo-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-6-[(3,5-difluorophenyl)oxy]-3-pyridinesulfonamide	574

6		6-{[3,4-bis(methyloxy)phenyl]oxy}-5-bromo-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-3-pyridinesulfonamide	598
7		5-bromo-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-6-{[3-(methyloxy)phenyl]oxy}-3-pyridinesulfonamide	568
8		5-bromo-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-6-{[4-(methyloxy)phenyl]oxy}-3-pyridinesulfonamide	568
9		5-bromo-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-6-[(3,4-dichlorophenyl)oxy]-3-pyridinesulfonamide	606
10		5-bromo-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-6-[(2,3-dichlorophenyl)oxy]-3-pyridinesulfonamide	606

EXAMPLE 11

Formulations for pharmaceutical use incorporating compounds of the present invention can be prepared in various forms and with numerous excipients. Examples of such formulations are given below.

Tablets/Ingredients	Per Tablet
1.Active ingredient (Cpd of Form. I)	40 mg
2.Corn Starch	20 mg
3.Alginic acid	20 mg
4.Sodium Alginate	20 mg
5.Mg stearate	1.3 mg
	2.3 mg

Procedure for tablets:

Step 1: Blend ingredients No. 1, No. 2, No. 3 and No. 4 in a suitable mixer/blender.

Step 2: Add sufficient water portion-wise to the blend from Step 1 with careful mixing after each addition. Such additions of water and mixing until the mass is of a consistency to permit its conversion to wet granules.

Step 3: The wet mass is converted to granules by passing it through an oscillating granulator using a No. 8 mesh (2.38 mm) screen.

Step 4: The wet granules are then dried in an oven at 140°F (60°C) until dry.

Step 5: The dry granules are lubricated with ingredient No. 5.

Step 6: The lubricated granules are compressed on a suitable tablet press.

Inhalant Formulation

A compound of Formula I, (1 mg to 100 mg) is aerosolized from a metered dose inhaler to deliver the desired amount of drug per use.

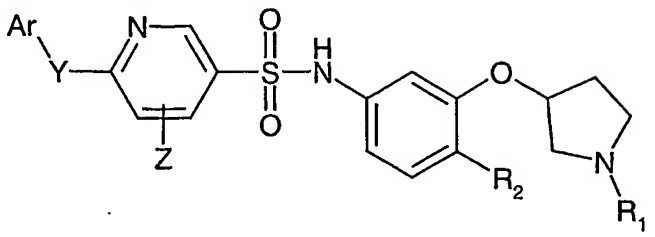
Parenteral Formulation

A pharmaceutical composition for parenteral administration is prepared by dissolving an appropriate amount of a compound of formula I in polyethylene glycol with heating. This solution is then diluted with water for injections Ph Eur. (to 100 ml). The solution is then sterilized by filtration through a 0.22 micron membrane filter and sealed in sterile containers.

The above specification and Examples fully disclose how to make and use the compounds of the present invention. However, the present invention is not limited to the particular embodiments described hereinabove, but includes all modifications thereof within the scope of the following claims. The various references to journals, patents and other publications which are cited herein comprise the state of the art and are incorporated herein by reference as though fully set forth.

What is claimed is:

1. A compound of Formula (I):



Formula (I)

wherein:

Ar is phenyl substituted or unsubstituted by one or two of the following: halogen, CN, $S(C_{1-6}$ alkyl), CF_3, OCF_3, SCF_3, C_{1-6} alkyl, C_{1-6} alkoxy, $CO_2(C_{1-6}$ alkyl), or NO_2;

Y is O or S;

Z is hydrogen, halogen, or C_{1-6} alkyl

R_2 is hydrogen, halogen, CN, or C_{1-4} alkyl;

R_1 is hydrogen or C_{1-6} alkyl;

or a pharmaceutically acceptable salt thereof.

2. A compound of claim 1 wherein Ar is substituted with one or two halogen or C_{1-6} alkoxy; Z is halogen or hydrogen; R_2 is halogen or hydrogen; and R_1 is C_{1-3} alkyl.

3. A compound of claim 1 chosen from:

5-bromo-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-6-[(2,3-dichlorophenyl)thio]-3-pyridinesulfonamide;

5-bromo-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-6-[(3,5-dichlorophenyl)thio]-3-pyridinesulfonamide;

6-{[3,4-bis(methyloxy)phenyl]thio}-5-bromo-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-3-pyridinesulfonamide;

5-bromo-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-6-[(3,5-dichlorophenyl)oxy]-3-pyridinesulfonamide;

5-bromo-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-6-[(3,5-difluorophenyl)oxy]-3-pyridinesulfonamide;

6-{[3,4-bis(methyloxy)phenyl]oxy}-5-bromo-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-3-pyridinesulfonamide;

5-bromo-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-6-{[3-(methyloxy)phenyl]oxy}-3-pyridinesulfonamide;

5-bromo-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-6-{[4-(methyloxy)phenyl]oxy}-3-pyridinesulfonamide;

5-bromo-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-6-[(3,4-dichlorophenyl)oxy]-3-pyridinesulfonamide; and

5-bromo-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)-6-[(2,3-dichlorophenyl)oxy]-3-pyridinesulfonamide.

4. A pharmaceutical composition comprising a compound of formula (I) of claim 1 and a pharmaceutically acceptable carrier or excipient.

5. A method of treating conditions associated with Urotensin-II imbalance by antagonizing the Urotensin-II receptor which comprises administering to a patient in need thereof, a compound of Formula I of claim 1.

6. A method according to Claim 5 wherein the disease is congestive heart failure, stroke, ischemic heart disease , angina, myocardial ischemia, cardiac arrhythmia, essential and pulmonary hypertension, renal disease, acute and chronic renal failure, end stage renal disease, peripheral vascular disease, male erectile dysfunction, diabetic retinopathy, intermittent claudication/ischemic limb disease, ischemic/hemorrhagic stroke, COPD, restenosis, asthma, neurogenic inflammation, migraine, metabolic vasculopathies, bone/cartilage/joint diseases, arthritis and other inflammatory diseases, fibrosis, pulmonary fibrosis, sepsis, atherosclerosis, dyslipidemia, addiction, schizophrenia, cognitive disorders, Alzheimers disease, impulsivity, anxiety, stress, depression, parkinsons, movement disorders, sleep-wake cycle, incentive motivation, pain, neuromuscular function, diabetes, gastric reflux, gastric motility disorders, ulcers and genitourinary diseases.

7. A method of treating conditions associated with Urotensin-II imbalance by antagonizing the Urotensin-II receptor which comprises administering to a patient in need thereof, a compound of Formula I of claim 3.

8. A method according to Claim 7 wherein the disease is congestive heart failure, stroke, ischemic heart disease , angina, myocardial ischemia, cardiac arrhythmia, essential and pulmonary hypertension, renal disease, acute and chronic renal failure, end stage renal disease,

peripheral vascular disease, male erectile dysfunction, diabetic retinopathy, intermittent claudication/ischemic limb disease, ischemic/hemorrhagic stroke, COPD, restenosis, asthma, neurogenic inflammation, migraine, metabolic vasculopathies, bone/cartilage/joint diseases, arthritis and other inflammatory diseases, fibrosis, pulmonary fibrosis, sepsis, atherosclerosis, dyslipidemia, addiction, schizophrenia, cognitive disorders, Alzheimers disease, impulsivity, anxiety, stress, depression, parkinsons, movement disorders, sleep-wake cycle, incentive motivation, pain, neuromuscular function, diabetes, gastric reflux, gastric motility disorders, ulcers and genitourinary diseases.

9. A pharmaceutical composition comprising a compound of formula (I) of claim 3 and a pharmaceutically acceptable carrier or excipient.